VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cognitive Function After the Initiation of Adjuvant Endocrine Therapy in Early-Stage Breast Cancer: An Observational Cohort Study

Patricia A. Ganz, Laura Petersen, Steven A. Castellon, Julienne E. Bower, Daniel H.S. Silverman, Steven W. Cole, Michael R. Irwin, and Thomas R. Belin

Patricia A. Ganz, Thomas R. Belin, Fielding School of Public Health, University of California, Los Angeles; Patricia A. Ganz, Laura Petersen, Jonsson Comprehensive Cancer Center, University of California, Los Angeles; Patricia A. Ganz, Daniel H.S. Silverman, Steven W. Cole, Michael R. Irwin, David Geffen School of Medicine, University of California, Los Angeles; Steven A. Castellon, VA Greater Los Angeles Health Care System; Steven A. Castellon, Julienne E. Bower, University of California, Los Angeles; Julienne E. Bower, Steven W. Cole, Michael R. Irwin, Cousins Center for Psychoneuroimmunology, Semel Institute, University of California, Los Angeles, Los Angeles, CA.

Published online ahead of print at www.jco.org on September 29, 2014.

Supported by funding from the National Cancer Institute Grant No. R01-CA109650 and the Breast Cancer Research Foundation (P.A.G.), Grants No. R01-AG034588, R01-AG026364, R01-CA119159, R01-HL079955, R01-HL095799, P30-AG028748, UL RR 033176 (M.R.I.), and the Cousins Center for Psychoneuroimmunology (M.R.I.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Patricia A. Ganz, MD, Division of Cancer Prevention and Control Research, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, A2-125 CHS, Box 956900, Los Angeles, CA 90095-6900; e-mail: pganz@mednet.ucla.edu.

0732-183X/14/3231w-3559w/$20.00

DOI: 10.1200/JCO.2014.56.1662

ABSTRACT

Purpose
This report examines cognitive complaints and neuropsychological (NP) testing outcomes in patients with early-stage breast cancer after the initiation of endocrine therapy (ET) to determine whether this therapy plays any role in post-treatment cognitive complaints.

Patients and Methods
One hundred seventy-three participants from the Mind Body Study (MBS) observational cohort provided data from self-report questionnaires and NP testing obtained at enrollment (T1, before initiation of ET), and 6 months later (T2). Bivariate analyses compared demographic and treatment variables, cognitive complaints, depressive symptoms, quality of life, and NP functioning between those who received ET versus not. Multivariable linear regression models examined predictors of cognitive complaints at T2, including selected demographic variables, depressive symptoms, ET use, and other medical variables, along with NP domains that were identified in bivariate analyses.

Results
Seventy percent of the 173 MBS participants initiated ET, evenly distributed between tamoxifen or aromatase inhibitors. ET-treated participants reported significantly increased language and communication (LC) cognitive complaints at T2 ($P = .003$), but no significant differences in NP test performance. Multivariable regression on LC at T2 found higher LC complaints significantly associated with T1 LC score ($P < .001$), ET at T2 ($P = .004$), interaction between ET and past hormone therapy (HT) ($P < .001$), and diminished improvement in NP psychomotor function ($P = .05$). Depressive symptoms were not significant ($P = .10$).

Conclusion
Higher LC complaints are significantly associated with ET 6 months after starting treatment and reflect diminished improvements in some NP tests. Past HT is a significant predictor of higher LC complaints after initiation of ET.

J Clin Oncol 32:3559-3567. © 2014 by American Society of Clinical Oncology

INTRODUCTION

During the past decade, there has been increased attention to the impact of cancer treatments on cognitive functioning after breast cancer.[1-6] Initial studies attributed cognitive difficulties to chemotherapy.[7,8] Emerging data suggest that all components of cancer treatment may put patients at risk and that there may also be pretreatment impairment.[9-12] Few studies have examined the impact of adjuvant endocrine therapy (ET) on cognitive functioning.[13,14] The Mind Body Study (MBS) was designed to address this question by recruiting a prospective cohort of patients with breast cancer at the end of primary treatment and before the initiation of adjuvant ET.[12] This report examines cognitive functioning outcomes in the MBS cohort 6 months later after the initiation of ET to determine whether this therapy plays any role in post-treatment cognitive complaints.

PATIENTS AND METHODS

Study Participants and Procedures

The MBS cohort was recruited primarily using rapid case ascertainment from the Los Angeles County SEER registry to identify patients recently diagnosed with breast cancer for invitation to participate in the study.[12] Study eligibility criteria included female age 21 to 65 years; newly diagnosed with stage 0, I, II, IIIA breast cancer; completed primary breast cancer treatments within the past 3

months; have not started ET; available for 12-month follow-up; English-language proficiency. Ineligibility and exclusions included standard risk factors for preexisting cognitive impairment; prior cancer treatment; active autoimmune disease or insulin-dependent diabetes; chronic use of steroid or hormone therapy (eg, estrogen, progestin compounds) other than vaginal estrogen.[12] Exclusions related to hormones and inflammatory conditions were required as a result of other MBS aims focused on the biology of cognitive dysfunction. Consenting women were invited to participate in three separate in-person assessments that were performed at baseline (T1) before the initiation of ET if prescribed, 6 months (T2), and 12 months later (T3). Assessments included self-administered questionnaires, neuropsychological (NP) testing, and blood tests—all performed at each time point (described in earlier articles[12,15]). This report focuses on self-reported cognitive complaints at T2. The research was approved by the University of California, Los Angeles institutional review board, and all participants provided written informed consent.

Demographic, Clinical Information, and Symptoms

Information was obtained from self-report and medical record abstraction. The Beck Depression Inventory II (BDI-II) assessed depressive symptoms during the 2 weeks preceding the study visit[16] with higher scores indicating more severe symptoms. We administered the RAND 36-item short form health survey (SF-36) as a measure of health-related quality of life[17-19] and report the physical and mental component scores.[20]

Cognitive complaints were assessed with the Patient's Assessment of Own Functioning Inventory (PAOFI),[21] a self-report instrument with prior evidence for correlation with neuropsychological test changes in patient samples.[13,22,23] The PAOFI contains 33 questions and is divided into four subscales: memory, higher-level cognition, language and communication (LC), and motor sensory processing. Details of the scoring method used in the MBS are summarized in a previous article.[12]

NP Assessments

NP testing was conducted by a trained technician, supervised by a licensed clinical neuropsychologist, using procedures previously published.[15] The 120-minute test battery was administered at T1 and T2. NP test scores were standardized to z-scores, with positive scores indicating outcomes better than age-corrected normative scores, with a mean of 0 and standard deviation of 1, and negative scores reflecting lower-than-normative performance.[24] Domain scores reflect average z-scores across each NP outcome included within the domain. These scores were used to create NP test domains on the basis of prior factor-analytic studies of larger NP data sets, as well as on groupings used in other studies with this cohort[25] (Appendix Table A1, online only). In addition, we examined the association between results from a verbal fluency task (F-A-S)[26] and cognitive complaints associated with ET. The Wechsler Test of Adult Reading, an estimate of full-scale intelligence quotient (IQ), was administered only at T1.

Statistical Analyses

Our primary goal was to evaluate whether the initiation of ET after T1 had any effect on recovery from cognitive complaints that were present at the end of primary treatment. We first compared patients receiving and not receiving ET at T2 on medical and demographic characteristics, the BDI-II, and SF-36, as well as PAOFI and NP scores, using χ^2, *t*-tests, or Wilcoxon rank-sum tests. This approach identified significantly higher complaints on the PAOFI LC subscale among women receiving ET. Additional bivariate analyses were conducted to examine which variables were associated with higher LC scores, using a score greater than one standard deviation above the mean of healthy women to classify higher than normal complaints[12] using χ^2 tests, *t*-tests, and analyses of variance to compare groups; significantly associated variables ($P < .10$) were included in regression models. Multivariable linear regression models examined predictors of LC scores at T2, including selected demographic and treatment variables (model 1), adding longitudinal change scores for the NP domains identified in bivariate analyses (model 2), with a final model that controlled for depressive symptoms at T2 (model 3). Age and IQ were included as covariates for all NP analyses. Change in NP score between T1 and T2 was chosen to take advantage of the longitudinal design, given that NP functioning was expected to improve over time as a result of practice effects and recovery from primary treatment effects. Additional multivariable modeling explored possible differences in outcomes across type of ET, comparing tamoxifen (TAM) versus aromatase inhibitors (AI). For the multivariable linear regression analyses, the PAOFI LC score was transformed using a [log(1 + x)] transformation because of non-normality of the unadjusted scores. All statistical tests were two-sided, and all analyses were conducted using SAS 9.4 (Cary, NC).

RESULTS

Participant Characteristics

One hundred eighty-nine women had data available at T1 before the initiation of ET if planned. Figure 1 shows participant flow and attrition between T1 and T2. For this analysis, we include the 173 participants for whom complete outcome data were available at T2, performing covariate-adjusted analyses using the 169 participants with complete data for all covariates. Comparing the 173 women in the T2 sample with the 16 women enrolled at T1 and not assessed at T2, we found that those who completed T2 evaluations were more likely to be married (68% *v* 38%; $P = .02$) and had greater income (63% *v* 31% with income > $100,000; $P = .02$) with no other significant differences.

Study sample characteristics are listed in Table 1 classified according to use of ET at T2. One hundred twenty-two (70%) of the 173 women were taking ET, with 50% receiving TAM, 47% receiving an AI, and the remainder receiving ovarian suppression therapy. Significant differences between the ET and no-ET groups were time since last treatment (shorter for ET, $P < .001$), type of treatment received (eg, chemotherapy and radiation; $P < .001$); and stage at diagnosis ($P = .005$). There were no significant differences in physical or mental functioning (SF-36), nor depressive symptoms (BDI-II), at either time point.

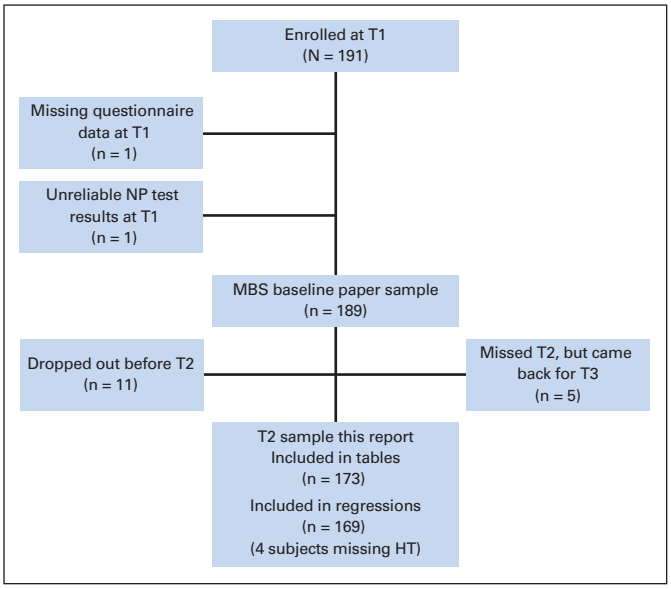

Fig 1. Flow diagram of participant enrollment from the Mind Body Study (MBS) cohort included in this article. HT, hormone therapy; NP, neuropsychological; T1, before initiation of endocrine therapy; T2, 6 months after initiation of endocrine therapy; T3, 12 months after initiation of endocrine therapy.

Table 1. Patient Characteristics According to Use of ET at T2

Characteristic	Total Sample at T1 (n = 173)		Total Sample at T2 (n = 173)		No ET at T2 (n = 51)				ET at T2 (n = 122)				T1 *P**	T2 *P**
					At T1		At T2		At T1		At T2			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Age, years													.60	.60
Mean	51.9		52.4		51.4		51.9		52.1		52.6			
SD	8.1		8.1		8.7		8.7		7.9		7.9			
Time since diagnosis, months													.69	.49
Mean	6.0		12.5		6.1		12.7		5.9		12.4			
SD	2.7		2.7		2.9		2.9		2.5		2.6			
Time since last treatment, months													**< .001**	**< .001**
Mean	1.2		7.7		1.9		8.5		0.9		7.3			
SD	1.0		1.2		1.1		1.3		0.8		1.0			
BMI													.42	.55
Mean	25.5		25.3		26.0		25.7		25.3		25.1			
SD	5.3		5.2		5.0		4.9		5.4		5.3			
Race			NA				NA				NA		.59†	NA
White, non-Hispanic	140	81			40	78			100	82				
Hispanic	15	9			4	8			11	9				
Black	5	3			3	6			2	2				
Asian	8	5			2	4			6	5				
Other	5	3			2	4			3	2				
Marital status			NA				NA				NA		.94	NA
Married	118	68			35	69			83	68				
Not married	55	32			16	31			39	32				
Education														
Post college	91	53			26	51			65	53				
College	52	30	NA		14	27	NA		38	31	NA		.62	NA
No college degree	30	17			11	6			19	17				
IQ													.15	NA
Mean	114.2		NA		112.7		NA		114.9		NA			
SD	8.9		NA		10.1		NA		8.3		NA			
Employment status														
Full or part-time	109	63	NA		33	65	NA		76	62	NA		.76	NA
Not employed	64	37			18	35			46	38				
Annual household income														
≥ $100,000	107	63	NA		29	58	NA		78	65	NA		.39	NA
< $100,000	63	37			21	42			42	35				
Surgery			NA				NA				NA		.06	NA
Mastectomy	60	35			23	45			37	30				
Lumpectomy	113	65			28	55			85	70				
Treatment			NA				NA				NA		**< .001**‡	NA
Chemotherapy and radiation	70	40			18	35			52	43				
Chemotherapy only	20	12			4	8			16	13				
Radiation only	58	34			13	25			45	37				
Neither	25	14			16	31			9	7				
Anthracycline use (n = 90; if received chemotherapy)			NA				NA				NA		.13	NA
Yes	22	24			8	36			14	21				
No	68	76			14	64			54	79				
Trastuzumab use at baseline			NA				NA				NA			NA
Yes	25	14			6	12			19	16			.52	
No	148	86			45	88			103	84				
Stage at diagnosis			NA				NA				NA		**.005**	NA
0	23	13			14	27			9	7				
I	80	46			19	37			61	50				
II	54	31			13	25			41	34				
III	16	9			5	10			11	9				

(continued on following page)

Table 1. Patient Characteristics According to Use of ET at T2 (continued)

Characteristic	Total Sample at T1 (n = 173)		Total Sample at T2 (n = 173)		No ET at T2 (n = 51)				ET at T2 (n = 122)				T1 P^*	T2 P^*
					At T1		At T2		At T1		At T2			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Previous HT			NA				NA				NA			NA
Yes	51	30			12	25			39	33			.30	
No	118	70			37	75			81	68				
Menopausal status at T1			NA				NA				NA		.48	NA
Pre- or perimenopausal	81	47			26	51			55	45				
Postmenopausal	92	53			25	49			67	55				
Time since LMP, months			NA				NA				NA		.50	NA
Mean	62.6				70.7				59.3					
SD	86.5				107.4				76.5					
Endocrine type at T2 (n = 122; if received ET)			NA		NA		NA				NA		NA	NA
Tamoxifen	61	50.0							61	50				
Aromatase inhibitor	57	47.0							57	47				
Ovarian suppression	4	3.0							4	3				
SF-36														
PCS													.41	.35
Mean	45.7		49.8		46.6		48.8		45.4		50.2			
SD	9.1		8.5		8.6		8.2		9.4		8.6			
MCS													.39	.39
Mean	49.3		49.7		50.2		50.7		48.9		49.3			
SD	9.3		9.5		8.6		9.3		9.5		9.6			
BDI-II													.92	.55
Mean	8.7		8.5		8.8									
SD	6.8		6.9		7.0									
PAOFI§														
Total													.79	.20
Mean	3.3		3.7		3.2		2.9		3.4		4.0			
SD	4.5		4.7		4.1		4.1		4.7		5.0			
Memory													.97	.30
Mean	1.5		1.4		1.5		1.2		1.5		1.5			
SD	2.1		2.0		2.2		1.8		2.1		2.0			
Higher-level cognition													.26	.19
Mean	0.6		0.7		0.4		0.5		0.7		0.8			
SD	1.5		1.6		1.2		1.5		1.6		1.7			
Language and communication													.40	**.009**
Mean	1.0		1.3		1.0		0.8		0.9		1.5			
SD	1.3		1.7		1.2		1.2		1.4		1.8			
Motor/sensory processing													.78	.12
Mean	0.3		0.3		0.3		0.4		0.3		0.3			
SD	0.6		0.6		0.5		0.7		0.7		0.6			
NP test¶														
Verbal learning													.54	.78
Mean	0.52		0.62		0.56		0.61		0.51		0.63			
SD	0.6		0.7		0.7		0.7		0.6		0.7			
Verbal memory													.45	.68
Mean	0.72		1.10		0.68		1.07		0.74		1.11			
SD	0.6		0.6		0.5		0.5		0.6		0.6			
Visual learning													.90	.20
Mean	0.01		−0.03		−0.00		−0.14		0.01		0.02			
SD	0.7		0.7		0.8		0.7		0.6		0.6			
Visual memory													.21	.61
Mean	−0.03		0.02		0.04		−0.02		−0.05		0.04			
SD	0.8		0.8		0.7		0.7		0.8		0.9			

(continued on following page)

Table 1. Patient Characteristics According to Use of ET at T2 (continued)

Characteristic	Total Sample at T1 (n = 173)		Total Sample at T2 (n = 173)		No ET at T2 (n = 51)				ET at T2 (n = 122)				T1 P*	T2 P*
					At T1		At T2		At T1		At T2			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Visuospatial function													.45	.06
Mean	−0.31		−0.21		−0.38		−0.35		−0.28		−0.15			
SD	0.7		0.6		0.7		0.7		0.7		0.6			
Psychomotor speed													.27	.29
Mean	0.52		0.71		0.63		0.79		0.47		0.68			
SD	0.6		0.6		0.6		0.6		0.7		0.7			
Executive function													.85	.65
Mean	0.35		0.53		0.32		0.45		0.36		0.57			
SD	0.8		0.8		0.7		0.7		0.8		0.8			
Motor speed													.32	.60
Mean	−0.24		0.09		−0.14		0.07		−0.28		0.10			
SD	1.0		1.0		1.1		1.0		0.9		1.0			

NOTE. Bold font indicates $P \leq .05$.
Abbreviations: BDI-II, Beck Depression Inventory II; BMI, body mass index; ET, endocrine therapy; HT, hormone therapy; IQ, intelligence quotient; LMP, last menstrual period; MCS, mental component scale; NA, not applicable; NP, neuropsychological; PAOFI, Patient's Assessment of Own Functioning Inventory; PCS, physical component scale; SD, standard deviation; SF-36, 36-item short form healthy survey.
*Comparing values between no ET and ET.
†White *v* nonwhite.
‡Although there is a significant difference ($P < .001$) when comparing all four treatment categories at once, there is no significant difference between chemotherapy and no chemotherapy ($P = .13$). There is a significant difference between radiation and no radiation ($P = .01$).
§Because the PAOFI variables are not normally distributed, *P* values in the table are the result of *t*-tests performed on log(1 + x). Results of nonparametric Wilcoxon rank-sum tests on the PAOFI values reported in the table were similar (*P* values not shown).
¶Unadjusted; however, *P* values reflect adjustment for age, IQ, and treatment type.

We also compared the characteristics of women who received TAM versus AI therapy (Appendix Table A2, online only). AI recipients were significantly older, more likely to have used hormone therapy (HT) in the past, and more often postmenopausal at T1 (all $P < .001$), with significant differences in education ($P = .01$). Physical functioning was also significantly lower ($P = .001$), as expected given the age difference. There were no significant differences between patients treated with AI and with TAM on the BDI-II or PAOFI scores.

Cognitive Functioning

Cognitive functioning was assessed by self-report and NP testing. Table 1 shows the comparison of the PAOFI total and subscales scores and NP domain scores at T1 and T2 by ET status. There was no significant difference by ET status at T2 for the mean PAOFI total score or its subscale scores, with the exception of the LC subscale score, for which the ET group had significantly higher complaints ($P = .009$). NP domain scores did not differ significantly according to ET, before or after controlling for differences in chemotherapy and radiation treatment (data not shown). Bivariate examination of the NP domains by AI or TAM use (Appendix Table A2), adjusted for age at T2, IQ, and treatment, showed slower psychomotor speed and motor speed in the AI patients compared with TAM patients.

Next we examined the bivariate relationships in women with higher and normal level PAOFI LC complaints at T2 using the variables examined in Table 1 (Appendix Table A3, online only). The following were found to be significantly associated with higher LC scores at T2 and were identified for inclusion in subsequent regression models: ET ($P = .004$), past HT ($P = .09$), shorter time since diagnosis ($P = .04$), and higher BDI-II score ($P = .001$). Those with higher LC complaints at T2 had significantly poorer performance on psychomotor speed (0.48 *v* 0.82; $P = .01$) and executive function (0.28 *v* 0.65; $P = .02$) NP domains at T2.

Multivariable Models Predicting LC Complaints at T2

Table 2 shows successive models regressing log-transformed LC scores at T2 on relevant predictor variables. Model 1 includes age, IQ, chemotherapy and radiation, time from last treatment to T1, past use of HT, T1 LC score as well as ET use at T2 and the interaction between past HT and ET. Model 2 adds the change in NP domain scores between T1 and T2 for the psychomotor and executive function domains. In model 3, we control for depressive symptoms by adding the BDI-II scores. In model 1, the following were significant: T1 LC score, the combination of past HT and ET at T2, and ET at T2 without past use of HT. In model 2, the initially significant variables remained, with a reduced change in psychomotor NP domain score as significantly associated with higher LC at T2 ($P = .02$). Adding the BDI-II to model 3 made no substantive changes to model 2, and depressive symptoms were not significant. We fit an additional model with an interaction between ET and the T1 to T2 psychomotor score; when the additional term was added, both the interaction and the primary effect of the T1 to T2 psychomotor score became nonsignificant. Figures 2A and 2B show scatterplots of the NP psychomotor domain change score and the associated PAOFI LC score at T2, according to receipt of ET. Lower scores (ie, fewer complaints) on the LC at T2 are associated with greater change (improvement) in NP score, with a significant correlation ($r = −0.19$; $P = .04$) only for patients who received ET (Fig 2B).

Given the patterns of association between ET and past HT, we fit separate models that included indicators for AI and TAM therapy, as

Table 2. Regressions of LC PAOFI Scores at T2

Variable	Regressions of Log(1 + T2 PAOFI LC score) (n = 169)					
	Model 1: Demo/Med Only*		Model 2: Add 2 NP Domains†		Model 3: Add BDI-II‡	
	Parameter Estimate	*P*	Parameter Estimate	*P*	Parameter Estimate	*P*
Intercept	0.81	.21	0.56	.39	0.50	.44
Log(1 + T1 PAOFI LC score)	0.54	**< .001**	0.56	**< .001**	0.54	**< .001**
T1 age	0.00	.65	0.00	.59	0.00	.52
T1 IQ (WTAR)	−0.01	.07	−0.01	.18	−0.01	.18
Prior treatment						
Chemotherapy and radiation	−0.01	.96	0.02	.87	−0.00	.98
Chemotherapy alone	0.11	.52	0.12	.49	0.07	.70
Radiation alone	−0.08	.60	−0.08	.60	−0.10	.49
Time since last treatment to T1, months	0.02	.75	0.02	.75	0.01	.83
ET and past HT						
Both ET and HT	0.56	**< .001**	0.58	**< .001**	0.55	**< .001**
ET only	0.35	**.003**	0.34	**.003**	0.33	**.004**
HT only	0.34	.06	0.34	.06	0.31	.08
Change in NP domain from T1 to T2 (+ = better)						
Psychomotor			−0.26	**.02**	−0.23	**.05**
Executive function			0.08	0.43	0.09	.33
T2 BDI-II					0.01	.10

NOTE. Bold font indicates $P \leq .05$.
Abbreviations: BDI-II, Beck Depression Inventory II; ET, endocrine therapy; HT, previous hormone therapy; IQ, intelligence quotient; LC, language and communication; NP, neuropsychological; PAOFI, Patient's Assessment of Own Functioning Inventory; T1, before initiation of endocrine therapy; T2, 6 months after initiation of ET; WTAR, Wechsler Test of Adult Reading.
*R^2, 0.38; model *F* value, 9.7; $P < .001$.
†R^2, 0.40; model *F* value, 8.7; $P < .001$.
‡R^2, 0.41; model *F* value, 8.3; $P < .001$.

well as an HT interaction term for each of the therapies (Appendix Tables A4 and A5, online only). In models including TAM and AI indicators (Appendix Table A4), both were significant and consistent with the findings in Table 2. In models that included interaction terms between type of ET and past HT, only the interaction between past HT and AI was statistically significant (Appendix Table A5), yet past HT alone was also significant ($P = .05$).

We performed additional regression models that included the verbal fluency NP test results using the Controlled Oral Word Association Test (F-A-S), given the specific nature of the LC complaints associated with ET at T2. Using the change in F-A-S score between T1 and T2, higher LC scores at T2 were negatively correlated with the F-A-S change score ($P = .02$) along with ET at T2 ($P = .006$), interaction between ET at T2 and prior HT ($P = .004$), depression ($P = .04$), and T1 LC score ($P < .001$), with model $R^2 = 0.41$ (data not shown).

DISCUSSION

ETs for breast cancer are widely prescribed and are an important component of standard adjuvant therapy. Clinically, TAM and AIs are fairly well-tolerated, although the need to take therapy for 5 or more years is associated with nonadherence and reduced benefit.[27-30] Reporting of cognitive difficulties after breast cancer treatment varies substantially, and the ability to attribute post-treatment complaints to specific therapies has been complicated by limited data on the potential contribution of ET. The validity of self-reported cognitive complaints has been questioned,[22,31] and until recently, only NP testing was considered a valid measure of cognitive functioning. However, the advent of sensitive neuroimaging studies has increased the ability to link functional imaging changes with both self-reported complaints and NP testing.[32] Thus, in the MBS cohort we examined both of these outcomes.

Studies in healthy women have demonstrated a positive relationship between estradiol levels, verbal memory, and verbal fluency[33-39]; for example, improved verbal fluency associated with changes in estradiol between the follicular and luteal phases of the normal menstrual cycle.[39] Given these and other reported salutary effects of estrogen on cerebral function, occurrence of adverse cognitive effects from adjuvant ET would not be surprising.[40] In the MBS, we examined both self-reported and objective assessments of cognitive function before and after initiation of ET. At T2, women who had initiated ET reported significantly higher LC complaints than those who did not receive ET. These complaints were represented by PAOFI items such as "Is it easier to have people show you things than it is to have them tell you about things?," "How often do you have difficulty thinking of the names of things," and "How often do you have difficulty thinking of the words [other than names] for what you want to say." These were the most frequently endorsed LC items at T2, ranging from 43% to 24% of the sample. In multivariable regression models, the significant predictors of higher LC score at T2 (greater LC complaints) were the T1 LC score, ET at T2, the combination of past use of HT with current use of ET, as well as less improvement (change) in the psychomotor speed NP domain score. Diminished performance in this NP domain may be related to the underlying LC complaints. Slowed processing speed limits the rate of intake of spoken information, which might be expected to adversely impact a person's ability to comprehend more complex or voluminous conversations. Our finding of less improvement in the verbal fluency (F-A-S) score in

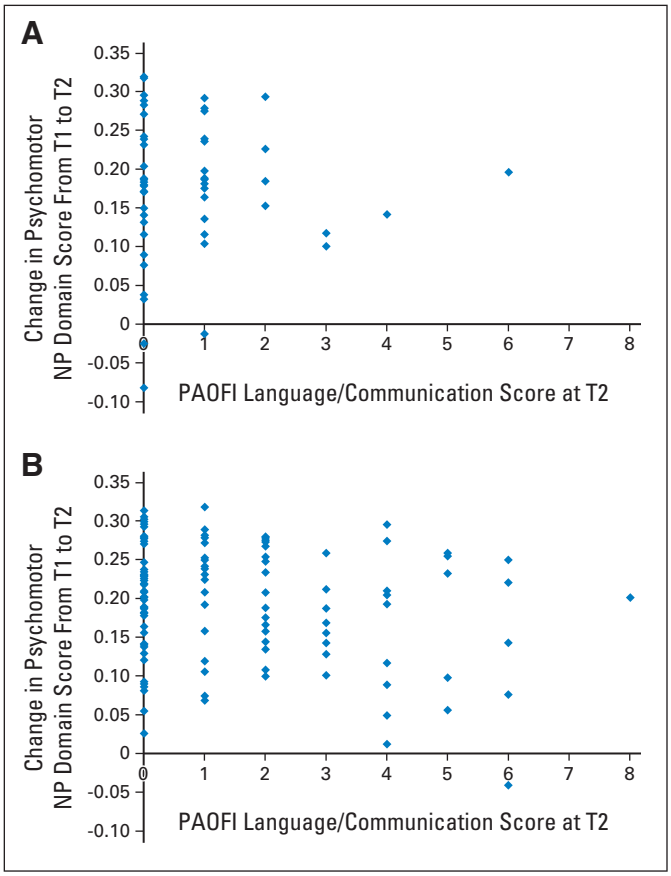

Fig 2. Scatterplots examining the relationship between T2 Patient's Assessment of Own Functioning Inventory (PAOFI) language and communication (LC) score (raw score) and the change in age and intelligence quotient–adjusted neuropsychological (NP) psychomotor domain score for individual participants from T1 (before initiation of endocrine therapy) to T2 (6 months after initiation of endocrine therapy). An NP change score greater than 0 indicates improvement. Correlations reported are based on the log-transformed LC PAOFI score. (A) For the 51 participants who did not receive endocrine therapy, $r = 0.00$ and $P = .98$, indicating no significant relationship between higher LC complaints and the change in NP psychomotor function between T1 and T2. (B) For the 122 participants who received endocrine therapy, $r = -0.19$ and $P = .04$, indicating a significant relationship with higher LC complaints associated with smaller improvements in NP psychomotor function between T1 and T2.

association with higher LC complaints at T2 is consistent with a hypothesized effect of adjuvant ET through lowered serum estradiol with AI therapy or direct effects of TAM binding to estrogen receptors in the brain.

Several small prospective studies found that initiation of ET was associated with significant changes in NP performance.[11,13,41,42] Schilder et al[43] found greater memory complaints among patients with breast cancer than healthy control participants in a small cross-sectional study of patients participating in the TEAM (Tamoxifen and Exemestane Multicenter) trial, assessed with self-report and NP testing approximately 2 years after starting either TAM or AI after adjuvant chemotherapy. There were no significant differences regarding NP testing between the two ETs. A larger prospective evaluation was conducted in 179 Dutch postmenopausal patients with breast cancer without chemotherapy exposure (mean, age 68 years) participating in the TEAM study and 120 healthy controls, with pretreatment and 1 year after ET NP evaluations.[14] The authors noted worse NP memory and executive function scores among TAM recipients compared with controls and slower processing speed among TAM users compared with the AI group. Although past HT data was available, its association with NP testing was not reported. Hurria et al[44] conducted a small prospective study of AI therapy comparing 35 older patients with breast cancer to healthy control participants from pretreatment to 6 months later. Although there were no significant differences in NP function between the two groups, for a small substudy sample who underwent positron emission tomography brain imaging, specific changes in metabolic activity in the medial temporal lobes were observed in association with AI therapy.

The MBS examined the course of cognitive recovery after primary adjuvant therapy in patients with breast cancer. At T1, before the start of ET, increased memory and executive complaints were reported in approximately one quarter of the cohort.[12] In this analysis, ET was not associated with memory or executive complaints at T2, nor was chemotherapy or radiation associated with the higher LC complaints that emerged at T2. The identification of previous exposure to HT and its interaction with ET in the multivariable regression models is a novel finding and may help to identify women who are potentially at greater risk for LC complaints in this setting. In secondary exploration of the effects of TAM compared with AI therapy, the interaction with previous HT was only significant for AI therapy, although only a small number of TAM users (n = 6) had received past HT. Hormonal effects on the brain are complex, and it is possible that prior exogenous HT (and its withdrawal) may prime the brain to be more susceptible to the effects of ET. Overall, these results have important clinical implications for counseling patients who may complain of increased difficulty in verbal communication after starting ET. Validation of their complaints may be clinically reassuring. Additional research is necessary to confirm our finding of a relationship between diminished recovery of psychomotor speed and ET as a possible mechanism for these specific complaints.

Limitations of this study include the young age of the sample (mean, approximately age 52 years) compared with the population of patients with breast cancer, the lack of prechemotherapy assessments, and the lack of a concurrent healthy control comparison group; however, for the latter, we had relevant normative reference data for the PAOFI and NP tests.[24] In addition, we focused primarily on self-reported cognitive complaints, given the modest effects of adjuvant treatments on NP tests in post-treatment survivors of breast cancer.[45] We believe this is one of the first studies to examine the course of cognitive functioning before and after the initiation of ET using concurrent control patients with breast cancer who have not received ET.

The MBS cohort is providing new insights into the potential mechanisms influencing cognitive complaints after breast cancer treatments.[12,15,46] Similar results are emerging from a prospective study of cognitive function in women with early-stage breast cancer at the University of California, San Francisco where adjuvant ET was found to be a risk factor for cognitive decline independent of other treatment and demographic factors.[47] This study also documented a significant association between perceived cognitive

difficulties and subsequent decrease in objective NP test performance. We hope that accumulating data from multiple studies will identify risk factors for cognitive difficulties after breast cancer treatment, and that with tailored therapies and cognitive rehabilitation strategies,[48] we can effectively diminish this feared complication of breast cancer treatments.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Patricia A. Ganz, Steven A. Castellon, Julienne E. Bower, Daniel H.S. Silverman, Steven W. Cole, Michael R. Irwin, Thomas R. Belin
Financial support: Patricia A. Ganz
Administrative support: Patricia A. Ganz
Provision of study materials or patients: Patricia A. Ganz
Collection and assembly of data: Patricia A. Ganz
Data analysis and interpretation: Patricia A. Ganz, Laura Petersen, Steven A. Castellon, Thomas R. Belin
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Ahles TA, Saykin AJ, McDonald BC, et al: Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: Impact of age and cognitive reserve. J Clin Oncol 28:4434-4440, 2010

2. Ahles TA: Brain vulnerability to chemotherapy toxicities. Psychooncology 21:1141-1148, 2012

3. Ahles TA, Root JC, Ryan EL: Cancer- and cancer treatment–associated cognitive change: An update on the state of the science. J Clin Oncol 30:3675-3686, 2012

4. Schagen SB, Vardy J, Steering Committee of the International Cognition and Cancer Task Force: Cognitive dysfunction in people with cancer. Lancet Oncol 8:852-853, 2007

5. Mandelblatt JS, Hurria A, McDonald BC, et al: Cognitive effects of cancer and its treatments at the intersection of aging: What do we know; what do we need to know? Semin Oncol 40:709-725, 2013

6. Castellon SA, Ganz PA, Bower JE, et al: Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. J Clin Exp Neuropsychol 26:955-969, 2004

7. van Dam FS, Schagen SB, Muller MJ, et al: Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy. J Natl Cancer Inst 90:210-218, 1998

8. Schagen SB, van Dam FS, Muller MJ, et al: Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 85:640-650, 1999

9. Scherling C, Collins B, Mackenzie J, et al: Prechemotherapy differences in response inhibition in breast cancer patients compared to controls: A functional magnetic resonance imaging study. J Clin Exp Neuropsychol 34:543-560, 2012

10. Ahles TA, Saykin AJ: Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 7:192-201, 2007

11. Collins B, Mackenzie J, Stewart A, et al: Cognitive effects of hormonal therapy in early stage breast cancer patients: A prospective study. Psychooncology 18:811-821, 2009

12. Ganz PA, Kwan L, Castellon SA, et al: Cognitive complaints after breast cancer treatments: Examining the relationship with neuropsychological test performance. J Natl Cancer Inst 105:791-801, 2013

13. Bender CM, Sereika SM, Berga SL, et al: Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology 15:422-430, 2006

14. Schilder CM, Seynaeve C, Beex LV, et al: Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: Results from the neuropsychological side study of the Tamoxifen and Exemestane Adjuvant Multinational trial. J Clin Oncol 28:1294-1300, 2010

15. Ganz PA, Bower JE, Kwan L, et al: Does tumor necrosis factor-alpha (TNFalpha) play a role in post-chemotherapy cerebral dysfunction? Brain Behav Immun 30:S99-S108, 2013 (suppl)

16. Beck AT, Steer RA, Brown GK: Beck Depression Inventory Manual (2nd ed). Boston, MA, Harcourt Brace, 1996

17. Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-483, 1992

18. McHorney CA, Ware JE Jr, Raczek AE: The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31:247-263, 1993

19. Hays RD, Sherbourne CD, Mazel RM: The RAND 36-item health survey 1.0. Health Econ 2:217-227, 1993

20. Ware JE Jr, Kosinki M, Keller SD: SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA, The Health Institute, 1994

21. Chelune CJ, Heaton RK, Lehman RAW: Neuropsychological and personality correlates of patients' complaints of disability, in Goldstein G, Tarter RE (eds): Advances in Clinical Neuropsychology (vol 3). New York, NY, Plenum Press, 1986, pp 95-126

22. Pullens MJ, De Vries J, Roukema JA: Subjective cognitive dysfunction in breast cancer patients: A systematic review. Psychooncology 19:1127-1138, 2010

23. Bender CM, Pacella ML, Sereika SM, et al: What do perceived cognitive problems reflect? J Support Oncol 6:238-242, 2008

24. Collins B, Mackenzie J, Kyerematenteng C: Study of the cognitive effects of chemotherapy: Considerations in selection of a control group. J Clin Exp Neuropsychol 35:435-444, 2013

25. Tulsky DS, Price LR: The joint WAIS-III and WMS-III factor structure: Development and cross-validation of a six-factor model of cognitive functioning. Psychological Assessment 15:149-162, 2003

26. Tombaugh TN, Kozak J, Rees L: Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol 14:167-177, 1999

27. Partridge AH, LaFountain A, Mayer E, et al: Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 26:556-562, 2008

28. Partridge AH, Wang PS, Winer EP, et al: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 21:602-606, 2003

29. Hershman DL, Kushi LH, Shao T, et al: Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 28:4120-4128, 2010

30. Hershman DL, Shao T, Kushi LH, et al: Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 126:529-537, 2011

31. Ganz PA: "Doctor, will the treatment you are recommending cause chemobrain?" J Clin Oncol 30:229-231, 2012

32. Pomykala KL, de Ruiter MB, Deprez S, et al: Integrating imaging findings in evaluating the post-chemotherapy brain. Brain Imaging Behav 7:436-452, 2013

33. Kampen DL, Sherwin BB: Estrogen use and verbal memory in healthy postmenopausal women. Obstet Gynecol 83:979-983, 1994

34. Carlson LE, Sherwin BB: Higher levels of plasma estradiol and testosterone in healthy elderly men compared with age-matched women may protect aspects of explicit memory. Menopause 7:168-177, 2000

35. Phillips SM, Sherwin BB: Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 17:485-495, 1992

36. Sherwin BB, Henry JF: Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: A critical review. Front Neuroendocrinol 29:88-113, 2008

37. Maki PM, Freeman EW, Greendale GA, et al: Summary of the National Institute on Aging-sponsored conference on depressive symptoms and cognitive complaints in the menopausal transition. Menopause 17:815-822, 2010

38. Maki PM, Dennerstein L, Clark M, et al: Perimenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life. Brain Res 1379:232-243, 2011

39. Maki PM, Rich JB, Rosenbaum RS: Implicit memory varies across the menstrual cycle: Estrogen effects in young women. Neuropsychologia 40:518-529, 2002

40. Buwalda B, Schagen SB: Is basic research providing answers if adjuvant anti-estrogen treatment of breast cancer can induce cognitive impairment? Life Sci 93:581-588, 2013

41. Jenkins V, Shilling V, Fallowfield L, et al: Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. Psychooncology 13:61-66, 2004

42. Jenkins V, Shilling V, Deutsch G, et al: A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer 94:828-834, 2006

43. Schilder CM, Eggens PC, Seynaeve C, et al: Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: Cross-sectional findings from the neuropsychological TEAM-side study. Acta Oncol 48:76-85, 2009

44. Hurria A, Patel SK, Mortimer J, et al: The effect of aromatase inhibition on the cognitive function of older patients with breast cancer. Clin Breast Cancer 14:132-140, 2014

45. Jim HS, Phillips KM, Chait S, et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol 30:3578-3587, 2012

46. Pomykala KL, Ganz PA, Bower JE, et al: The association between pro-inflammatory cytokines, regional cerebral metabolism, and cognitive complaints following adjuvant chemotherapy for breast cancer. Brain Imaging Behav 7:1-13, 2013

47. Rugo HS, DeLuca AN, Heflin L, et al: Prospective study of cognitive function (cog fcn) in women with early-stage breast cancer (ESBC): Predictors of cognitive decline. J Clin Oncol 31:418s, 2013 (suppl 15; abstr 6620)

48. Rugo HS, Ahles T: The impact of adjuvant therapy for breast cancer on cognitive function: Current evidence and directions for research. Semin Oncol 30:749-762, 2003

Acknowledgment

We thank the women who volunteered for this study, as well as the Los Angeles County SEER registry and the many Los Angeles area physicians for assisting us in recruitment; Amy Oppenheim and Lorna Kwan for their role in data collection and data management.

Appendix

Table A1. NP Testing Battery*

Cognitive Domain	NP Measure	Outcome Variable
Estimated IQ	WTAR	Standard score
Verbal learning	CVLT-2	List A, total score; learning slope
Verbal memory	WMS-3	logical memory, immediate, total score; logical memory, delay, total score; logical memory, percent retention
Visual learning	BVMT-R	Trails 1-3 total score; learning score
Visual memory	BVMT-R	Delayed recall; percent retention
Visuospatial function	ROCF, WAIS-3	Complex figure copy score; block design, total score
Psychomotor speed	WAIS-3, Trails, Stroop	Digit symbol, raw score; Trails A, completion time; Stroop color naming, completion time
Executive function	Halstead-Reitan	Trails B completion time; Stroop interference trial, completion time
	WAIS-3	Letter-number sequencing raw score
Motor speed/dexterity	Grooved pegboard	Nondominant, completion time; dominant, completion time

Abbreviations: BVMT-R, Brief Visuospatial Memory Test (revised); CVLT-2, California Verbal Learning Test, (2nd ed); IQ, intelligence quotient; NP, neuropsychological; ROCF, Rey Osterreith Complex Figure; Trails, Trailmaking Test, Parts A and B; WAIS-3, Wechsler Adult Intelligence Scale (3rd ed); WMS-3, Wechsler Memory Scale (3rd ed); WTAR, Wechsler Test of Adult Reading.

*NP test scores were standardized to z-scores, with positive scores indicating outcomes better than age-corrected normative scores (with a mean of 0 and standard deviation of 1) and negative scores reflecting lower-than-normative performance. Domain scores reflect average z-scores across each NP outcome included within the domain.

Table A2. Patient Characteristics According to Type of Endocrine Therapy at T2 (only those patients [n = 118] who were using either tamoxifen or aromatase inhibitors)

Characteristic	Tamoxifen at T2 (n = 61)		Aromatase Inhibitor at T2 (n = 57)		*P*
	No.	%	No.	%	
Age at T2, years					**< .001**
Mean	47.9		58.6		
SD	6.5		3.8		
Time since diagnosis at T2, months					.92
Mean	12.3		12.3		
SD	2.6		2.7		
Time since last treatment at T2, months					.06
Mean	7.5		7.2		
SD	1.0		0.9		
BMI at T2					.72
Mean	25.0		25.4		
SD	5.5		5.1		
Race					.13*
White, non-Hispanic	47	77	50	88	
Hispanic	7	11	4	7	
Black	2	3	0	0	
Asian	4	7	1	2	
Other	1	2	2	4	
Marital status					.35
Married	39	64	41	72	
Not married	22	36	16	28	
Education					**.01**†
Post college	29	48	33	58	
College	26	43	11	19	
No college degree	6	10	13	23	
Employment status					.64
Full or part-time	40	66	35	61	
Not employed	21	34	22	39	
Annual household income					.07
≥ $100,000	44	73	32	57	
< $100,000	16	27	24	43	
Surgery					.12
Mastectomy	22	36	13	23	
Lumpectomy	39	64	44	77	
Treatment					.17
Chemotherapy and radiation	21	34	28	49	
Chemotherapy only	11	18	4	7	
Radiation only	23	38	22	39	
Neither	6	10	3	5	
Anthracycline use (if chemotherapy received; n = 64)					1.0
Yes	7	22	7	22	
No	25	78	25	78	
Trastuzumab use at baseline					.88
Yes	9	15	9	16	
No	52	85	48	84	
Stage at diagnosis					.11
0	8	13	1	2	
I	31	51	29	51	
II	17	28	22	39	
III	5	8	5	9	
Previous HT					**< .001**
Yes	6	10	32	57	
No	54	90	24	43	
Menopausal status at T1 (no data for T2)					**< .001**
Pre- or perimenopausal	47	77	4	7	
Postmenopausal	14	23	53	93	

(continued on following page)

Table A2. Patient Characteristics According to Type of Endocrine Therapy at T2 (only those patients [n = 118] who were using either tamoxifen or aromatase inhibitors) (continued)

Characteristic	Tamoxifen at T2 (n = 61) No.	%	Aromatase Inhibitor at T2 (n = 57) No.	%	*P*
SF-36 at T2					**.001**
PCS					
Mean	52.7		47.7		
SD	7.3		9.2		
MCS					.39
Mean	48.6		50.1		
SD	9.8		9.2		
BDI-II at T2					.65
Mean	8.9		8.4		
SD	6.2		6.9		
PAOFI at T2					
Total					.27
Mean	3.5		4.5		
SD	4.3		5.7		
Memory					.71
Mean	1.5		1.6		
SD	1.8		2.2		
Higher-level cognition					.27
Mean	0.6		0.9		
SD	1.4		1.9		
Language and communication					.25
Mean	1.3		1.7		
SD	1.8		1.9		
Motor/sensory Processing					.14
Mean	0.2		0.3		
SD	0.5		0.7		
NP test‡					
Verbal learning					.44
Mean	0.69		0.54		
SD	0.6		0.7		
Verbal memory					.16
Mean	1.13		1.05		
SD	0.5		0.7		
Visual learning					.69
Mean	0.06		−0.02		
SD	0.6		0.7		
Visual memory					.30
Mean	0.01		0.06		
SD	0.8		0.9		
Visuospatial function					.53
Mean	−0.18		−0.12		
SD	0.6		0.6		
Psychomotor speed					.06
Mean	0.79		0.56		
SD	0.6		0.7		
Executive function					.09
Mean	0.66		0.47		
SD	0.7		0.8		
Motor speed					**.05**
Mean	0.31		−0.16		
SD	0.9		1.1		

NOTE. Bold font indicates $P \leq .05$.

Abbreviations: BDI-II, Beck Depression Inventory II; BMI, body mass index; IQ, intelligence quotient; LC, language and communication; MCS, mental component scale; NP, neuropsychological; PAOFI, Patient's Assessment of Own Functioning Inventory; PCS, physical component scale; SD, standard deviation; SF-36, 36-item short form healthy survey; T1, before initiation of endocrine therapy; T2, 6 months after initiation of endocrine therapy.

*White *v* nonwhite.

†Although there is a significant difference ($P = .01$) when comparing all 3 categories at once, there is no significant difference between post-college and less than post-college ($P = .78$).

‡Unadjusted; however, *P* values reflect adjustment for age, IQ, and treatment type.

Table A3. Patient Characteristics According to PAOFI LC Complaint Status* at T2

	T1					T2				
	High LC at T2 (n = 54)		Normal LC at T2 (n = 119)			High LC at T2 (n = 54)		Normal LC at T2 (n = 119)		
Demo/Med Variable	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Age, years					.31					.31
Mean	52.8		51.5			53.4		52.0		
SD	7.1		8.5			7.1		8.6		
Time since diagnosis, months					.98					.65
Mean	6.0		6.0			12.3		12.5		
SD	2.8		2.6			2.8		2.7		
Time since last treatment, months					.21					**.04**
Mean	1.0		1.2			7.4		7.8		
SD	1.1		1.0			1.3		1.2		
BMI					.30					.47
Mean	26.2		25.3			25.7		25.1		
SD	5.9		5.0			5.7		4.9		
Race					.26†					
White, non-Hispanic	41	76	99	83						
Hispanic	7	13	8	7						
Black	0	0	5	4						
Asian	3	6	5	4						
Other	3	6	2	2						
Marital status					.52					
Married	35	65	83	70						
Not married	19	35	36	30						
Education					.96					
Post college	28	52	63	53						
College	16	30	36	30						
No college degree	10	19	20	17						
IQ					.11					
Mean	112.6		114.9							
SD	8.8		8.9							
Employment status					.30					
Full or part-time	31	57	78	66						
Not employed	23	43	41	34						
Annual household income					1.0					
≥ $100,000	34	63	73	63						
< $100,000	20	37	43	37						
Surgery					.93					
Mastectomy	19	35	41	34						
Lumpectomy	35	65	78	66						
Treatment					.33					
Chemotherapy and radiation	24	44	46	39						
Chemotherapy only	9	17	11	9						
Radiation only	15	28	43	36						
Neither	6	11	19	16						
Anthracycline use (if received chemotherapy)					.97					
Yes	8	24	14	25						
No	25	76	43	75						
Trastuzumab use at baseline					.31					
Yes	10	19	15	13						
No	44	81	104	87						
Stage at diagnosis					.32					
0	4	7	19	16						
I	27	50	53	45						
II	16	30	38	32						
III	7	13	9	8						
Previous HT					.09					
Yes	20	39	31	26						
No	31	61	87	74						

(continued on following page)

Table A3. Patient Characteristics According to PAOFI LC Complaint Status* at T2 (continued)

Demo/Med Variable	T1 High LC at T2 (n = 54) No.	T1 High LC at T2 (n = 54) %	T1 Normal LC at T2 (n = 119) No.	T1 Normal LC at T2 (n = 119) %	T1 P	T2 High LC at T2 (n = 54) No.	T2 High LC at T2 (n = 54) %	T2 Normal LC at T2 (n = 119) No.	T2 Normal LC at T2 (n = 119) %	T2 P
Menopausal status at T1					.28					
Pre- or perimenopausal	22	41	59	50						
Postmenopausal	32	59	60	50						
Time since LMP, months					.61					
Mean	67.7		60.3							
SD	87.8		86.2							
ET at T2										
Yes						46	85	76	64	**.004**
No						8	15	43	36	
Endocrine type at T2 (if ET received)										.30‡
Tamoxifen						20	43	41	54	
Aromatase inhibitor						24	52	33	43	
Ovarian suppression						2	4	2	3	
SF-36										
PCS					**.009**					**.03**
Mean	42.8		47.1			47.4		50.8		
SD	10.5		8.2			10.1		7.5		
MCS					**< .001**					**< .001**
Mean	44.4		51.5			45.7		51.5		
SD	9.4		8.4			9.8		8.7		
BDI-II					**< .001**					**.001**
Mean	12.1		7.2			11.3		7.3		
SD	7.4		5.9			7.9		6.1		
PAOFI §										
Total					**< .001**					**< .001**
Mean	6.1		2.0			8.5		1.5		
SD	5.6		3.2			5.4		2.0		
Memory					**< .001**					**< .001**
Mean	2.5		1.0			2.9		0.8		
SD	2.4		1.8			2.3		1.3		
Higher-level cognition					**< .001**					**< .001**
Mean	1.4		0.2			1.8		0.2		
SD	2.1		0.8			2.3		0.7		
Language and communication					**< .001**					**< .001**
Mean	1.8		0.6			3.3		0.3		
SD	1.7		1.0			1.5		0.5		
Motor/sensory processing					**.02**					**.04**
Mean	0.5		0.2			0.5		0.2		
SD	0.9		0.4			0.9		0.5		
NP test¶										
Verbal learning					.67					.71
Mean	0.53		0.52			0.55		0.65		
SD	0.6		0.7			0.6		0.7		
Verbal memory					.51					.43
Mean	0.64		0.76			1.01		1.14		
SD	0.6		0.6			0.7		0.6		
Visual learning					.85					.20
Mean	−0.05		0.03			−0.15		0.03		
SD	0.6		0.7			0.6		0.7		
Visual memory					.95					.55
Mean	−0.06		−0.01			0.03		0.02		
SD	0.9		0.7			1.0		0.8		
Visuospatial function					.69					.58
Mean	−0.39		−0.27			−0.27		−0.18		
SD	0.7		0.7			0.7		0.6		

(continued on following page)

Table A3. Patient Characteristics According to PAOFI LC Complaint Status* at T2 (continued)

	T1					T2				
	High LC at T2 (n = 54)		Normal LC at T2 (n = 119)			High LC at T2 (n = 54)		Normal LC at T2 (n = 119)		
Demo/Med Variable	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Psychomotor speed					.14					**.01**
Mean	0.35		0.60			0.48		0.82		
SD	0.7		0.6			0.7		0.6		
Executive function					**.02**					**.02**
Mean	0.09		0.47			0.28		0.65		
SD	0.7		0.7			0.8		0.7		
Motor speed					.50					.25
Mean	−0.37		−0.18			−0.10		0.17		
SD	1.1		0.9			1.1		0.9		

NOTE. Bold font indicates $P \leq .05$.
Abbreviations: BDI-II, Beck Depression Inventory II; ET, endocrine therapy; HT, hormone therapy; IQ, intelligence quotient; LC, language and communication; LMP, last menstrual period; MCS, mental component scale; NP, neuropsychological; PAOFI, Patient's Assessment of Own Functioning Inventory; PCS, physical component scale; SF-36, 36-item short form healthy survey; SD, standard deviation; T1, before initiation of ET; T2, 6 months after initiation of ET.
*Women whose LC scores were within one standard deviation of healthy norms were categorized as Normal LC, while women whose LC scores were at least one standard deviation higher than healthy controls were categorized as High LC
†White *v* nonwhite.
‡Tamoxifen *v* aromatase inhibitor.
§Because the PAOFI variables are not normally distributed, *P* values are the result of *t*-tests performed on log(1 + x).
¶Unadjusted; however, *P* values reflect adjustment for age, IQ, and treatment.

Table A4. Regressions of Log Transformed T2 LC PAOFI Scores Including Separate Dummy Variables for Type of Endocrine Therapy and HT Separately Without Interaction

	Regressions of Log (1 + T2 PAOFI LC score; n = 165)					
	Model 1: Demo/Med Only*		Model 2: Add 2 NP Domains†		Model 3: Add BDI-II‡	
Variable	Parameter Estimate	*P*	Parameter Estimate	*P*	Parameter Estimate	*P*
Intercept	0.93	.16	0.70	.30	0.65	.33
Log(1 + T1 PAOFI LC score)	0.56	**< .001**	0.57	**< .001**	0.55	**< .001**
T1 age	−0.00	.94	−0.00	.98	0.00	.96
T1 IQ (WTAR)	−0.01	.08	−0.01	.20	−0.01	.19
Previous treatment						
Chemotherapy and radiation	−0.00	.98	0.02	.87	−0.00	1.0
Chemotherapy alone	0.07	.68	0.08	.65	0.04	.83
Radiation alone	−0.07	.64	−0.07	.64	−0.09	.54
Time since last treatment to T1, months	0.02	.66	0.02	.67	0.02	.73
Ever had HT	0.22	**.03**	0.25	**.02**	0.22	**.04**
Had TAM at T2	0.30	**.009**	0.29	**.01**	0.28	**.01**
Had AI at T2	0.36	**.004**	0.36	**.004**	0.36	**.004**
Change in NP domain from T1 to T2 (+ = better)						
Psychomotor			−0.26	**.03**	−0.23	**.05**
Executive function			0.08	.43	0.09	.34
T2 BDI-II					0.01	.16

NOTE. Bold font indicates $P \leq .05$.
Abbreviations: AI, aromatase inhibitor; BDI-II, Beck Depression Inventory II; HT, hormone therapy; IQ, intelligence quotient; LC, language and communication; NP, neuropsychological; PAOFI, Patient's Assessment of Own Functioning Inventory; TAM, tamoxifen; T1, before initiation of endocrine therapy; T2, 6 months after initiation of endocrine therapy; WTAR, Wechsler Test of Adult Reading.
*R^2, 0.39; model *F* value, 10.0; $P < .001$.
†R^2, 0.41; model *F* value, 8.9; $P < .001$.
‡R^2, 0.42; model *F* value, 8.4; $P < .001$.

Table A5. Regressions of Log Transformed T2 LC PAOFI Scores Including Type of Endocrine Therapy, HT, and the Interaction Between Them

	Regressions of Log (1 + T2 PAOFI LC score; n = 165)					
	Model 1: Demo/Med Only*		Model 2: Add 2 NP Domains†		Model 3: Add BDI-II‡	
Variable	Parameter Estimate	*P*	Parameter Estimate	*P*	Parameter Estimate	*P*
Intercept	1.02	.13	0.78	.25	0.73	.28
Log (1 + T1 PAOFI LC score)	0.56	**< .001**	0.58	**< .001**	0.56	**< .001**
T1 age	−0.00	.84	−0.00	.89	−0.00	.96
T1 IQ (WTAR)	−0.01	.06	−0.01	.16	−0.01	.15
Previous treatment						
Chemotherapy and radiation	−0.01	.94	0.02	.91	−0.01	.96
Chemotherapy alone	0.05	.76	0.06	.72	0.02	.91
Radiation alone	−0.06	.69	−0.06	.68	−0.08	.58
Time since last treatment to T1, months	0.03	.62	0.02	.64	0.02	.71
Had HT alone	0.38	**.04**	0.37	**.04**	0.35	**.05**
Had TAM alone	0.35	**.004**	0.34	**.006**	0.33	**.007**
Had AI alone	0.43	**.007**	0.42	**.008**	0.41	**.009**
Had TAM + HT	0.40	.09	0.44	.06	0.39	.10
Had AI + HT	0.62	**< .001**	0.63	**< .001**	0.61	**< .001**
Change in NP domain from T1 to T2 (+ = better)						
Psychomotor			−0.24	**.04**	−0.22	.07
Executive function			0.08	.42	0.09	.33
T2 BDI-II					0.01	.16

NOTE. Bold font indicates $P \leq .05$.
Abbreviations: AI, aromatase inhibitor; BDI-II, Beck Depression Inventory II; HT, hormone therapy; IQ, intelligence quotient; LC, language and communication; NP, neuropsychological; PAOFI, Patient's Assessment of Own Functioning Inventory; TAM, tamoxifen; T1, before initiation of endocrine therapy; T2, 6 months after initiation of endocrine therapy; WTAR, Wechsler Test of Adult Reading.
*R^2, 0.40; model *F* value, 8.4; $P < .001$.
†R^2, 0.42; model *F* value, 7.6; $P < .001$.
‡R^2, 0.43; model *F* value, 7.3; $P < .001$.